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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,646	05/14/2001	Nicholas C. Nicolaides	001107.00138	6480

22907 7590 03/19/2003

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EXAMINER	
SHUKLA, RAM R	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/19/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,646	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *8-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,10,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of the invention of group I, claims 1-7 in Paper No. 17 is acknowledged. The traversal is on the ground(s) that different classification does not demonstrate art recognized separate subject and that different searches will not be required. This is not found persuasive because classification is not the only basis for restriction. Applicants have listed a certain patent numbers and stated that they are classified in both 435/455 and 435/441. It is not clear as to how this point is relevant to the instant case since patent n0. 6479628 is not even classified in 435, rather it is classified in 530. Additionally, the class and subclass provide a way of grouping patents together based on general features or characteristics and being placed in one class or one subclass does not mean that the inventions are related. Next, the methods of groups I and III are different not only because the group III invention has additional step of adding mutagen, but the method of group I has yet another step, the step of restoring mismatch repair activity to the cell by decreasing expression of the dominant negative allele and no such step is required for practicing the method of group III. Therefore the search for the two methods will be separate and not coextensive.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8-50 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 17.

3. Claims 1-7 are under consideration.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention recites a method that uses a cell comprising a dominant negative allele of any mismatch repair gene under the control of an inducible transcriptional regulatory element. However, the specification only discloses a PMS2 truncation mutant PMS2134. There is no description of the structure of any other mutants of PMS2 that would have functioned as transdominant mutants or the structure of any other mismatch repair genes.

In analyzing whether the written description requirement is met for the genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification does not provide the structure of any other dominant negative mutant of any mismatch repair gene other than PMS2134. No other transdominant mutant alleles of PMS2 are disclosed.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed compositions because it is not known what are the different dominant negative mutants of mismatch repair genes or PMS2 other than PMS2134 and what particulars mutations, such as point mutations, deletion mutations or any other sequence changes would be present in any possible dominant negative mutants of PMS2 or other mismatch repair genes. One skilled

in the art would not have been able to predict the mutations required to change the wild type PMS2 gene into dominant mutant alleles. Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possessions of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

6. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to generate a mutation in a mammalian cell in vitro comprising growing a hypermutable mammalian cell comprising the gene of interest and a polynucleotide comprising PMS2134, does not reasonably provide enablement for an in vivo method or a method wherein a mammalian cell comprises any dominant negative mutant of PMS2 or of any mismatch repair (MMR) gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims.

The specification as filed is not enabling for an in vivo method or a method using a cell that comprises any dominant negative mutant alleles of any mismatch repair gene or PMS2 because the specification does not provide sufficient guidance as to how an artisan of skill would have made dominant negative alleles of any MMR genes or what is the structure of any dominant negative mutant alleles of MMR and whether such mutants would have functioned and produced hypermutable cells and mutated a gene of interest when expressed in a mammalian cell.

The primary issue is: will any mutant of any MMR gene function as a dominant negative allele and what mutations in any MMR gene would have produced a mutant that would have functioned as a dominant negative protein?

The specification teaches a truncation mutant of PMS2, PMS2134, which when expressed in a Syrian hamster fibroblast cells, cause the hypermutability to the cell and a plasmid pCAROF is used to test the mutation caused by the cell. When the expression of the PMS2134 is regulated using an inducible promoter, the mutation of the exogenously added gene can be regulated. When the expression of

the PMS2 dominant negative mutant is blocked, there is no mutation, however, when the expression of the dominant negative mutant is induced the mutation or correction of ORF in the test plasmid takes place (see working examples 1-3). It is noted that while other mutants of PMS2 are known, their dominant negative property is not described either in the art or in the specification. Additionally, there is no disclosure about the dominant negative mutant of any other MMR genes, though their mutants are known. For example, there are other mutants of PMS2, e.g. a mutant of PMS2 has been identified in which codons 268-669 is deleted. There is no disclosure if this PMS2 mutant would have functioned as a dominant mutant. Yet another mutant of PMS2 lacks codons 301-381, however there in no evidence present whether this mutant would have functioned as a dominant negative factor (see last para on page 75 continued on page 79 in Nicolaides et al Nature 371:75-80, 1994). The specification does not provide any guidance as to what other mutations or truncation of what other amino acids would have resulted in the production of PMS2 dominant mutant alleles so that they would have inhibited the mismatch repair function of the cells that would have expressed such mutants. Therefore, it is possible that any mutants of PMS2 may not function as dominant negative phenotype in a mammalian cell and the specification does not provide any guidance as to what specific mutations or deletion would have been required to change PMS2 or any other MMR gene to become a dominant negative protein.

In conclusion, the specification does not provide sufficient guidance to make and use dominant negative mutants of any MMR gene, which would have mutated a gene of interest in a mammalian cell. Further the specification does not provide any guidance as to whether any mutant of PMS2 or any other MMR would have functioned as a dominant negative protein in a mammalian cell. It is reiterated that the specification does not provide any disclosures of any other dominant negative alleles of a MMR, other than the truncation mutant of 133 amino acids of PMS2, named PMS2134 and the specification does not provide any guidance as to what mutations or deletions in a MMR gene would have changed it into a mutant negative proteins so that expression of such mutant proteins in a mammalian cell

would have made the cell hypermutable, which would have mutated a gene of interest. Therefore, It is concluded that the specification is not enabling for the invention as claimed and it would have required undue experimentation for an artisan to have practiced the invention commensurate with the full scope of the claims and therefore, limiting the scope of the claimed invention to a method to generate a mutation in a mammalian cell in vitro comprising growing a hypermutable mammalian cell comprising the gene of interest and a polynucleotide comprising PMS2134 is proper.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is not clear as to how the last step of restoring mismatch repair activity relevant to the method since the purpose of the method is to generate mutation and the last step does not have any thing to do with generating mutation. Accordingly, the metes and bounds of the claimed invention are not clear.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having

ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nicolaides et al 1998 Molecular and Cellular Biology 18:1635-1641) or Nicolaides et al (US Patent 6,146,894, 11-14-00, effective filing date 4-14-1998) in view of Bujard et al (WO 96/01313, 1-18-1996).

Nicolaides et al (MCB 1998) teaches stably transfected Syrian hamster TK-ts13 fibroblast cell lines that express wild type or mutant truncated human PMS2 protein that has 133 amino acids. These cell lines were created by transfecting the cells with PMS2 expression vectors that comprise the wild type PMS2 gene or the mutant PMS2 gene that has a thymidine at nt 424 of the wild type PMS2 gene and that results in the truncation of the protein at 134 producing a protein of 133 amino acids (see methods section). Nicolaides et al further teach that the cells expressing the truncated form of PMS2 have reduced mismatch repair efficiency and induced microsatellite instability (see the entire document), as revealed by tests using heteroduplex DNA substrates. Nicolaides et al also teach that the ability to inactivate mismatch repair activity of cells through the introduction of the human PMS2 truncation mutant that has the dominant negative phenotype may have practical values, for example, making other eukaryotic cells mismatch repair deficient. They further teach that this method of introducing mismatch repair in cells is better than knockout models. They also suggest that transgenosis with the human PMS2 mutant gene could prove to be useful in for creating mismatch repair in germ cells and somatic cells and might facilitate the production of highly diverse agriculture and livestock products (see last para of the section on discussion). The art also teaches that effect of the mismatch repair gene is evident when it is expressed in a sufficient concentration. The art does not teach to express the dominant mutant allele of MMR under inducible transcriptional regulatory sequences. The art also does not teach a method for mutating a gene of interest.

Nicolaides et al (6,146,984) teaches a method of producing a mutation in a gene of interest by growing a poulation of mammalian cells comprising the gene of interest and dominant negative allele of PMS2 and identifying the cell that harbors the mutation in the gene of interest (see claim 11). The art also teaches steps of identifying the mutation in the gene of interest (see claims 12-22). The art does not teach to express the dominant mutant allele of MMR under inducible transcriptional regulatory sequences.

Bujard et al teaches a method of regulating expression of genes in eukaryotic cells wherein the expression of the gene can be turned on or off by adding or removing tetracycline (see the abstract and the rest of the patent).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the expression vector of Nicolaides et al for expressing the dominant negative mutant of PMS2 as taught by Bujard et al with a reasonable expectation of success. An artisan of skill would have been motivated to use the expression system of Bujard et al because it would have provided a regulated expression of the dominant negative PMS2 and such would have been desired because the continuous expression of the dominant negative PMS2 would have resulted in high rate of mutation in the genomic DNA of the cell resulting in transformation. It is noted that the dominant negative PMS2 expression was known to cause cancer at the time of the invention.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this

application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D
PATENT EXAMINER